Journal of Cystic Fibrosis 23 (2024) 334–340

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Original Article

Global disparities in cystic fibrosis outcomes prior to CFTR modulators: A CF registries cohort study in South Africa and Canada

Marco Zampoli [a,b,*], Jenna Sykes [c], Janine Verstraete [a], Stephanie Y. Cheng [d], Brenda Morrow [a], Michael S. Pepper [e], Cheryl Stewart [f], Heather J. Zar [a,b], Anne L. Stephenson [c]

[a] Department of Paediatrics and Child Health, University of Cape Town, South Africa
[b] South African MRC Unit for Child and Adolescent Health, University of Cape Town, South Africa
[c] Department of Respirology, Adult Cystic Fibrosis Program, St. Michael's Hospital, University of Toronto, Toronto, Canada
[d] Cystic Fibrosis Canada, Toronto, Canada
[e] Department of Immunology, Institute for Cellular and Molecular Medicine, SAMRC Extramural Unit for Stem Cell Research and Therapy, University of Pretoria, South Africa
[f] Department of Basic Medical Sciences, The University of the West Indies, Mona, Jamaica

ARTICLE INFO

Keywords:
Outcome disparities
Cystic fibrosis
South Africa
Canada

ABSTRACT

Background: Outcomes of cystic fibrosis (CF) differ between low-middle income and high-income countries, but comparative data are lacking. We compared South African (SA) and Canadian CF outcomes to explore what disparities existed prior to access of CFTR modulators in Canada.

Methods: A cross-sectional study of SA and Canadian CF registries data for period 1 January to 31 December 2018. CF registry data were harmonised between countries to compare lung function and nutrition outcomes. Poor nutrition was defined as BMIz-score < -1 in children and < 18.5 kg/m^2 in adults. Standardised mean difference (SMD) >10 was considered significant.

Results: After excluding Canadians on CFTR modulators and lung transplant recipients, data on 4049 Canadian and 446 SA people was analysed. Compared to Canada, people in SA were younger (median age 15.8 years vs. 24.1 years: SMD 52) with fewer males (47.8% vs 54.2%; SMD 12.5) and White (70.9% vs. 93.3%; SMD 61.3). Class I-III *CFTR* mutation frequency was similar in SA (n = 384, 86.1%) and Canada (n = 3426, 84.9%). After adjusting for age, gender, diagnosis age, genotype, *P.aeruginosa* infection and pulmonary treatments, FEV1pp was 8.9% lower (95% CI 6.3% to 11.4%) and poor nutrition 1.7-fold more common (OR 1.70; 95% CI 1.19–2.41) in SA compared to Canada.

Conclusion: Lung function and nutrition was significantly lower in SA compared to Canada. Global disparities in CF outcomes between high and low-middle income countries are likely to widen as CFTR modulators are rapidly scaled up in only high-income countries.

1. Introduction

International cystic fibrosis (CF) registries from high income countries (HIC) have documented improving CF survival estimates over past decades [1]. Improving survival age is attributed to many factors including newborn screening (NBS), improved nutritional interventions, active surveillance, prevention and treatment of infections and organ transplantation [2]. In addition, novel cystic fibrosis transmembrane conductance regulator (CFTR) modulator drug therapy is anticipated to significantly further improve CF outcomes and survival [3,4]. In contrast to HIC, less is known about the epidemiology and outcomes of CF populations in low-and middle-income countries (LMIC) where conditions of poverty, poor healthcare infrastructure and limited resources to diagnose CF prevail. Furthermore, ethnicity and CF genotype differ significantly in LMIC compared to HIC with populations of predominately European descent [5,6]. Studies reporting *CFTR* mutation prevalence in Brazil and Africa have described higher rates of uncommon or novel mutations than HIC which may be an important determinant of CF outcomes in these settings [6,7]. However, factors such as socioeconomic status (SES), living conditions, delayed CF diagnosis, nutrition,

* Corresponding author at: Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital, Klipfontein Rd 5th floor ICH Building, Rondebsoch, Cape Town 7700, South Africa.
E-mail address: m.zampoli@uct.ac.za (M. Zampoli).

https://doi.org/10.1016/j.jcf.2023.09.003
Received 28 February 2023; Received in revised form 1 August 2023; Accepted 7 September 2023
Available online 12 September 2023

pulmonary infections, and limited access to expensive CF therapies may be more important determinates of CF outcomes in LMIC compared to HIC.

South Africa (SA) is a middle income country with a population of nearly 60 million with diverse ancestry and conditions of extreme socioeconomic disparity [8]. Healthcare infrastructure and services are provided through a resource-constrained public health system and well-resourced private healthcare. Newborn screening for CF is not available. Essential CF care and CF medications including pancreatic enzyme replacement therapy (PERT) are available, but expensive CF therapies such inhaled tobramycin solution, recombinant DNase are scarce and CFTR modulator therapies are not available. Poor nutrition, methicillin resistant staphylococcus aureus (MRSA) infection and non-White ancestry have all been associated with poorer CF outcomes in SA [9,10]. In contrast, Canada is a HIC with a population of almost 40 million. Universal healthcare including NBS for CF is provided for free which allows Canadians to access most CF medical care without additional personal financial costs. The majority of essential CF medications and lung transplants are paid for by government programs including the early CFTR modulator drugs (ivacaftor), prior to 2018 for a small number of people with CF (pwCF) who were eligible.

Examining differences in health outcomes between CF care centers has spawned a body of evidence focused on quality improvement initiatives in an effort to explain such differences and improve outcomes [11,1]. Similarly, international comparisons of the CF population through registries have led to important research to understand the driving factors contributing to disparate CF outcomes [12,13]. Comparing current CF health outcomes in SA and Canada, and factors that potentially explain any difference in outcomes, may be helpful for planning targeted interventions and advocating for improved access to novel therapies where outcomes are less favourable. We therefore harmonised data in the SA and Canadian CF registries to compare demographic, clinical and health outcomes characteristics between people with pwCF receiving care in SA and Canada at a time prior to when CFTR modulator therapy was more widely available in Canada.

2. Methods

2.1. Study design and populations

This is a cross-sectional cohort study of CF populations captured in the SA and Canadian CF registries for the calendar period 1 January to 31 December 2018. The Canadian CF Registry (CCFR) was developed in the 1970s and is managed by Cystic Fibrosis Canada. Consented data are entered into the CCFR by the 42 CF centers across Canada. Universal access to health care and incentivised data entry programs for participating CF centers within Canada ensures that the majority of pwCF are captured in the CCFR. The SA CF Registry (SACFR) is a public-private collaboration that was launched in 2018 and includes CF care centers at six university hospitals and several private practice clinics across SA with expertise in CF care. Consented annual review registry data is collected by independent data capturers covering different regions of SA, who extract and capture registry data from medical records at each participating clinic or practice. By 31 December 2018, it is estimated that over 80% of the known SA CF population in care was captured in the SA CF registry [9].

2.2. Harmonization of CF registry data

A combined data dictionary outlining variable definitions was systematically created using a mapping strategy in order to make data directly comparable (see on-line supplement). Demographic, CF diagnosis and genotype information were collected. Genotype was classified as homozygous F508del, heterozygous F508del, not F508del and missing. *CFTR* mutations were further categorised as class I- III and class IV-VI. Clinical information in 2018 on sputum microbiology, CF-related complications, CF therapies including number of courses of intravenous antibiotics, were recorded from both countries. Due to inability to harmonize most sputum microbiology data captured in the registries as a result of differing data collection definitions, sputum microbiology reporting was restricted to any isolate of *P.aeruginosa,* methicillin resistant *staphylococcus aureus* (MRSA) *and* non-tuberculous *mycobacterium species* (NTM).

2.3. Outcomes

Lung function (LF) was measured by forced expiratory volume in one second (FEV_1) expressed as a percentage of the predicted values (FEV_1pp) for healthy age, race and sex-matched controls using Global Lung Initiative (GLI) reference equations [14]. Non-White people in SA were entered as "Other" ethnicity in GLI equations in line with published guidelines [15]. In order to harmonize LF measurements, the highest recorded stable pre-bronchodilator FEV_1pp in 2018 for subjects six years and older were selected from the SA and Canadian registries as this is how FEV1pp is captured in the SA CF registry. Lung function impairment was classified as severe ($FEV_1pp \leq 40$), moderate (FEV_1pp 41–69), mild (FEV_1pp 70–89) and normal ($FEV_1pp \geq 90$). In the event of death, lung transplantation or starting CFTR modulator therapy in 2018, patients were included but the FEV_1pp measurements in 2018 prior to these events were included in analyses. People who started CFTR modulators, died or were transplanted prior to 2018 were excluded from formal analyses (Fig. 1).

Body mass index (BMI) measurements were selected from the same day as FEV_1 measurements. BMI z-scores (BMIz) were calculated for children 0–18 years using World Health Organization reference equations [16]. For individuals 18 years of age and older, BMI (kg/m^2) was calculated and classified according to World Health Organization guidelines. Poor nutrition was defined as BMIz $\langle$ -1 for age $<$ 18 years or BMI $<$ 18.5 kg/m^2 for age 18 years and older; overweight was defined as BMIz $\rangle$ 2 for age <18 years or BMI >24.9 kg/m^2 for age 18 years and older.

2.4. Statistical methods

Demographic and clinical variables were summarized by country, with categorical variables expressed as frequency and proportion, and continuous variables as means with standard deviation (SD) if parametric and medians with range if non-parametric. Differences between countries were compared using the Mann-Whitney test for continuous variables and the Chi-square test for categorical variables. Standardized mean difference (SMD) was calculated to identify statistically and clinically meaningful differences between the two countries, with a SMD of greater than 10 as the threshold [17]. The magnitude of difference in LF and poor nutrition between the two countries was estimated by linear regression and logistic regression, respectively. Confounders were chosen *a priori* based on clinical knowledge and prior literature and included: age, sex, genotype, diagnosis age, any *P. aeruginosa* infection, poor nutrition, and the pulmonary treatments recombinant human DNAse (rhDNAse) and macrolides. BMI was dichotomized as poor nutrition against the combined categories of adequate weight and overweight. Multiple imputation using chained equations was used to impute missing values for *P. aeruginosa* infection and pulmonary treatments. Ten imputed datasets were created and results were combined using Rubin's rules [18]. Statistical analysis was conducted using R version 4.0.3. All p-values are two-sided and assessed at $p<0.05$.

2.5. Ethical considerations

Approval has been obtained for the University of Cape Town Research Ethics Committee (HREC 032/2019) SA, and St. Michael's Hospital (REB 20–310), Toronto. Informed consent and assents were collected in SA and Canada accordance with local and institutional and

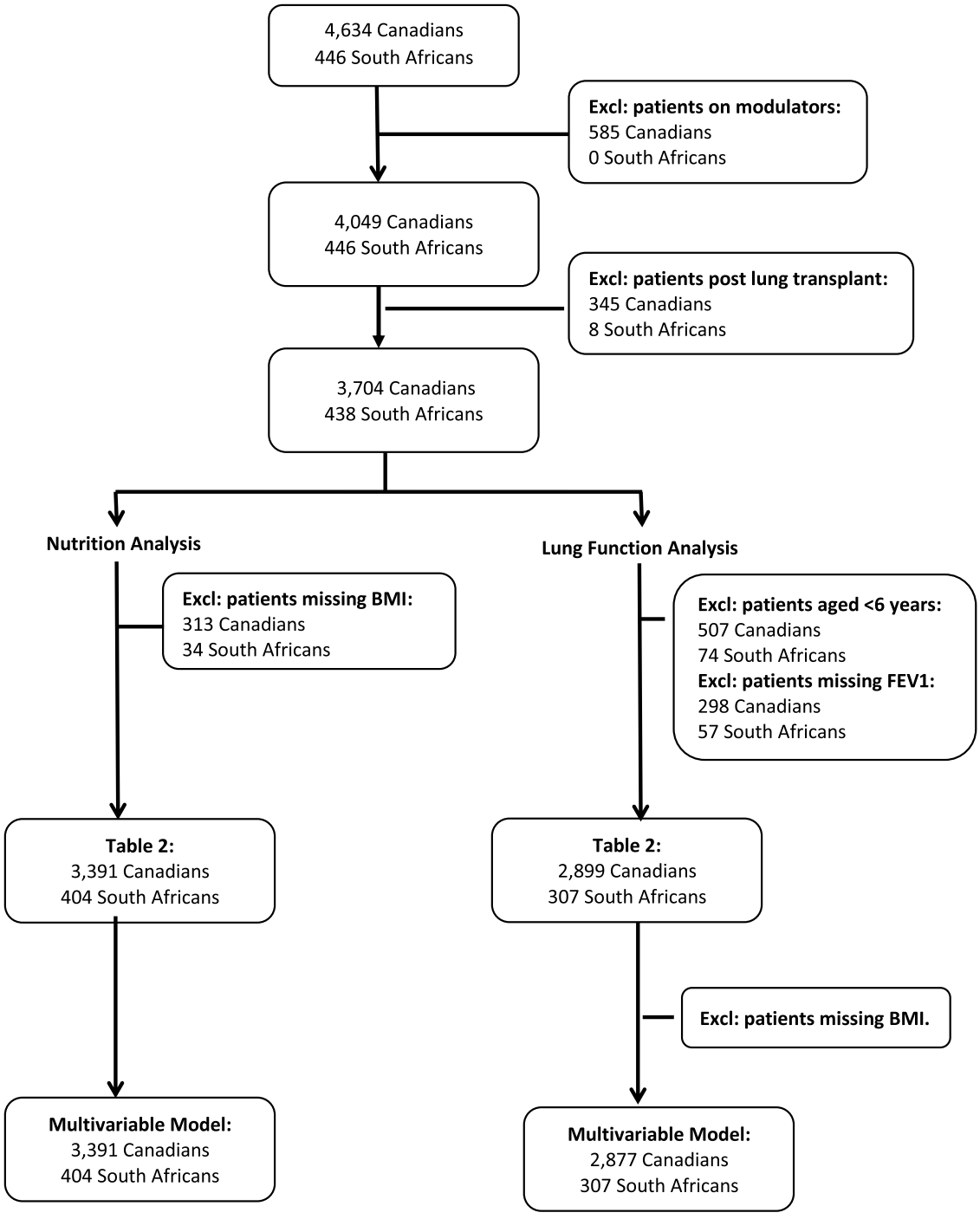

Fig. 1. Cohort flow diagram for Canadian and South African CF registry participant selection 01 January to 31 December 2018.

registry requirements.

3. Results

3.1. Demographic and diagnosis information

Data on 4049 Canadian and 446 SA pwCF in 2018 were analysed (Table 1 and Fig. 1). Compared to Canada, the CF population in SA was younger (median age 15.8 years vs. 24.1 years: SMD 52) with a lower proportion of males (47.8% vs 54.2%; SMD 12.5) and White people (70.9% vs. 93.3%; SMD 61.3). Age of CF diagnosis was slightly younger in Canada and more children were diagnosed by NBS in Canada compared to SA ($n = 550$, 13.6% vs $n = 1$, 0.2%, SMD 54.6); the one case in SA was diagnosed by NBS in California, USA, and the family relocated to SA. Poor nutrition at time of diagnosis was present significantly more in SA compared to Canada ($n = 131$, 53.5% vs $n = 1117$, 35.5%: SMD 36.8).

Sixty-one (1.3%) and 12 (2.7%) pwCF in Canada and SA, respectively, had incomplete genotyping recorded in the CF registries, Table 1. F508del was the most common *CFTR* mutation in both countries with similar proportions of people who were homozygous for F508del (SA 47.8% vs. Canada 42.4%). In SA, 3120+1G>*A* was the second most prevalent mutation (allele frequency 9.9%) and in Canada, 621+1G->*T* the second most prevalent mutation (allele frequency 2.0%). Overall, *CFTR* mutations class I-III were present with similar frequency in SA ($n = 384$, 86.1%) and Canada ($n = 3426$, 84.9%), Table 1.

Table 1
Demographic and diagnosis information among the CF population in Canada and South Africa, December 2018, excluding people on CFTR modulatory therapy.

	Canada (N = 4049)	South Africa (N = 446)	SMD
Sex: n (%)			
Female	1856 (45.8)	233 (52.2)	12.8
Male	2193 (54.2)	213 (47.8)	
Age in years, median (range)	24 (0.1–82.5)	15.8 (0–53.6)	52
Age in years: n (%)			
0–5.9 years	507 (12.5)	74 (16.6)	11.6
6–11.9 years	514 (12.7)	96 (21.5)	23.6
12–17.9 years	505 (12.5)	77 (17.3)	13.5
18–29.9 years	1061 (26.2)	121 (27.1)	2.1
≥ 30 years	1462 (36.1)	78 (17.5)	43
Race: n (%)			
White	3765 (93)	316 (70.9)	60
Mixed	28 (0.7)	85 (19.1)	64.7
Black African	34 (0.8)	41 (9.2)	39
Other/Unknown	222 (5.5)	4 (0.9)	26.3
Diagnosis age in years, median (range)	0.5 (0–75.8)	0.6 (0–47.8)	17.6
Diagnosis age in years: n (%)			
0–2	2696 (66.6)	307 (68.8)	4.8
2–18	1008 (24.9)	119 (26.7)	4.1
≥ 18	345 (8.5)	20 (4.5)	16.4
Newborn screening diagnosis: n (%)	550 (13.6)	1 (0.2)	54.6
Meconium ileus: n (%)	519 (12.8)	68 (15.2)	7.0
Nutritional status at diagnosis	n = 3146	n = 245	
Normal weight	1863 (59.2)	107 (43.7)	31.5
Poor Nutrition	1117 (35.5)	131 (53.5)	36.8
Overweight	166 (5.3)	7 (2.9)	12.3
Sweat test at diagnosis, mean (SD)			
sweat chloride test (mmol/L)	92.8 (23.8)	107.4 (21.9)	63.5
sweat conductivity (mmol/L)	N/A	105.8 (19.5)	N/A
no sweat test documented; n (%)	1879 (46.4)	152 (34.1)	25.3
Genotype: n (%)			
F508del:			
Homozygous	1715 (42.4)	213 (47.8)	10.9
Heterozygous	1774 (43.8)	145 (32.5)	23.4
Other	499 (12.3)	76 (17)	13.4
Missing /Incomplete genotyping (one or two unknown *CFTR* variants)	61 (1.5)	12 (2.7)	8.3
Mutation class: n (%)			
I – III	3426 (84.6)	384 (86.1)	7.8
IV- VI	502 (12.4)	44 (9.9)	
Missing/unclassified	121 (3)	18 (4)	5.7
Most common *CFTR* mutation allele frequencies: alleles, n (%)			
F508del	3436 (84.9)	358 (80.3)	N/A
3120+1G>*A*	0	44 (9.9)	
621+1G->*T*	80 (2.0)	0	
Unknown	65 (1.6)	12 (2.7)	
3272–26A>*G*	0	7 (1.6)	
Other	0	7 (1.6)	
G551D	0	3 (0.7)	
M1101K	41 (1.0)	0	
G542X	35 (0.9)	0	
711+1G->*T*	25 (0.6)	0	
A455E	21 (0.5)	5 (1.1)	
N1303K	21 (0.5)	5 (1.1)	
L206W	19 (0.5)	–	
3849+10kbC>T	0	1 (0.2)	
R1162X	0	1 (0.2)	
W1282X	15 (0.4)		

SMD: Standardized mean difference, values > 10 indicate clinically important differences.

3.2. Microbiology

P.aeruginosa was isolated in 2018 more frequently in SA than Canada (SA n = 192, 43.0% vs Canada n = 1458, 36.0%; SMD 26.3). Infection rates of MRSA and NTM were similar in both countries. Comparison of other infections or chronic infection status between countries could not be reliably determined due to different definitions and data capturing approaches.

3.3. Complications and CF therapies

The frequency of allergic bronchopulmonary aspergillosis (ABPA) and CF-related liver disease was similar in both countries, Table 2. CF-related diabetes (Canada 22.2% vs, SA 15.9%: SMD 12.7) and pancreatic sufficiency (Canada 18% vs, SA 10%; SMD 22) was more common in Canada than SA. Azithromycin and hypertonic saline inhalations were prescribed more frequently in SA and rhDNAse more frequently used in Canada, Table 2. More pwCF in SA than Canada received one or more courses of intravenous antibiotics (SA n = 202, 45.3% vs Canada n = 969, 23.9%: SMD 46.4). Three hundred and seventy-six (9.3%) pwCF in Canada had received a lung transplant in 2018 or earlier compared to 11 (2.5%) in SA.

3.4. Outcomes

Forty-two (1.0%) and three (0.7%) adults in Canada and SA died in 2018, respectively (Table 2). There were no deaths in children less than 18 years in either country in 2018. Details of the number of LF and nutrition measurements in 2018 in pooled analysis is presented in Fig. 1.

3.4.1. Lung function

Lung function was significantly lower across all ages in SA compared to Canada, including children 6–11.9 years age (Fig. 2). After adjusting for age, sex, genotype, diagnosis age, any *P. aeruginosa* infection, poor nutrition, and pulmonary treatments, FEV_1pp was 8.9% lower in SA compared to Canada (95% CI 6.3% to 11.4%; p-value <0.0001), Table 3. The impact of nutrition on LF did not differ significantly by country.

3.4.2. Nutrition

Poor nutrition was significantly more prevalent across all age groups in SA compared to Canada, (SA 91, 22.5% vs Canada 373, 11.0%: SMD 31.2) including children 0–5.9 years, Table 2, and Fig. 3. After adjusting for age, sex, genotype, diagnosis age and any *P. aeruginosa* infection, poor nutrition was 1.7-fold more common in SA compared to Canada (OR 1.70; 95% CI 1.19–2.41). Other factors associated with poor nutrition in both countries were age of diagnosis 2–18 years, *P. aeruginosa* and pulmonary treatments, Table 3.

4. Discussion

This registry-based study comparing health outcomes between SA and Canada has identified significant health disparities, specifically less favorable LF and nutrition outcomes in SA compared to Canada that are attributable to factors over and above age, CFTR mutation class, sex, diagnosis age, *P. aeruginosa* infection, lung transplantation and CFTR modulator therapy. A further observation is that these differences were already present in early childhood suggesting early life health factors may be important determinants for poorer outcomes observed in SA. This study was not specifically designed to identify which additional factors were associated with poorer outcomes in SA. However, it is reasonable to assume that these may include lower SES, inferior standards of CF care, limited access to publicly funded health care and expensive therapies such as rhDNase and inhaled tobramycin. Socio-economic conditions and quality of healthcare delivery are important determinants of CF outcomes, even in high income settings [19,20]. We could not include robust measures of SES as these were not captured by either registry. However, the gross domestic product per capita of Canada is 7-fold higher than SA which indirectly reflects the difference in healthcare expenditure between the countries [21]. Although lung transplant recipients and pwCF on CFTR modulators were excluded from the formal analyses, inclusion of these factors would likely contribute to a wider difference in observed health outcomes between SA and Canada. Documenting and monitoring differences in CF-related outcomes is important in advocacy for improved quality of CF care and equitable global access to CFTR modulators [22].

Table 2
Clinical, lung function and nutritional characteristics of CF registry populations in South Africa and Canada in 2018, excluding people on CFTR modulatory therapy.

	Canada ($N = 3391$)	South Africa ($N = 404$)	SMD
Microbiology: n (%)			
Any *P.aeruginosa*	1458 (36)	192 (43)	26.3
Missing	157 (3.9)	65 (14.6)	37.6
Any MRSA	243 (6)	28 (6.3)	5.5
Missing	157 (3.9)	80 (17.9)	46.3
Any NTM isolate:	197 (4.9)	5 (1.1)	21.2
Missing	157 (3.9)	77 (17.3)	44.6
Pulmonary therapies: n (%)			
Hypertonic saline	1523 (37.6)	211 (50.6)	26.4
Recombinant human DNase	1904 (47)	122 (29.2)	37.4
Inhaled Antibiotics	2250 (55.6)	224 (53.8)	3.5
Azithromycin	1527 (37.7)	335 (80.3)	96.2
Intravenous antibiotic courses in 2018			
0	3080 (76.1)	244 (54.7)	46.1
1	579 (14.3)	101 (22.6)	21.6
2	224 (5.5)	52 (11.7)	22
≥ 3	166 (4.1)	49 (11)	26.3
lung transplant recipients (2018 or earlier)	376 (9.3)	11 (2.5)	28.9
liver transplant recipients (2018 or earlier)	28 (0.7)	0 (0)	N/A
Complications/ comorbidity): n (%)			
ABPA	70 (1.8)	20 (5.2)	18.7
CF-related diabetes	900 (22.2)	71 (17.2)	12.7
CF-related liver disease with cirrhosis	135 (3.3)	22 (5.4)	10
Pancreatic insufficient	3310 (82.1)	377 (89.8)	22.1
Vital status in 2018			
Alive on 31 December 2018	4007 (99)	443 (99.3)	4
Died in 2018	42 (1)	3 (0.7)	4
Age at death (years): median (range)	33.7 (13.6–82.4)	36 (32–38)	7.4
Alive, but not seen in 2018	156 (3.9)	21 (4.7)	4.2
Nutritional status: n (%)			
Normal weight	2448 (72.2)	280 (69.3)	6.3
Overweight	570 (16.8)	33 (8.2)	26.4
Poor nutrition	373 (11.0)	91 (22.5)	31.2
Proportion with poor nutrition: n (%)			
F508del homozygous	186/1429 (13%)	38/194 (19.6%)	17.9
F508del heterozygous	137/1494 (9.2%)	32/133 (24.1%)	40.8
Class I-III mutation	328/2882 (11.4%)	79/353 (22.4%)	29.7
Class IV-V mutation	30/411 (7.3%)	7/35 (20%)	37.6
Lung function (age ≥ 6 years)	$n = 2899$	$n = 307$	
FEV_1pp: n (%)			
≥ 70	1962 (67.7)	171 (55.7)	24.8
40–69	705 (24.3)	101 (32.9)	19.1
< 40	232 (8)	35 (11.4)	11.5
FEV_1pp: Median (range)			
F508del homozygous	82.9 (61–98.7); $N = 1296$	78 (60.8–92.9); $N = 180$	15.6
F508del heterozygous	86.3 (61.3–100.2); $N = 466$	78 (53.1–92.7); $N = 64$	29.4
Other/missing genotype	84.9 (64.1–100.2); $N = 1435$	64.1 (51.7–85.8); $N = 120$	56.8
Class I-III mutation	83 (61.7–99.2); $N = 2650$	75.9 (56.2–90.1); $N = 310$	27.7
Class IV-V mutation	93 (71.1–103.2); $N = 438$	61.6 (51.4–85.1); $N = 40$	74.4

Legend Table 2:.
NTM: non-tuberculous mycobacterium.
FEV_1z: Forced expiratory volume in one second z-score.
FEV_1pp: Forced expiratory volume in one second percent predicted.
ABPA: allergic bronchopulmonary aspergillosis.
MRSA: methicillin resistant *S. aureus*.
SMD: Standardised mean difference, values >10 indicate clinically important differences.

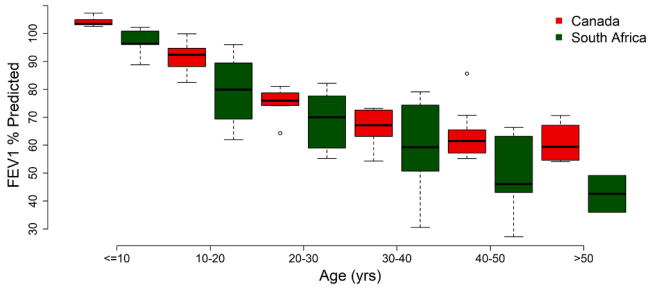

Fig. 2. Comparison of lung function (FEV1pp) by age categories (6 years and older) between the South African and Canadian CF Registry cohorts in 2018. Horizontal bar represents median value and boxes 25–75% IQR; maximum and minimum range end indicated by thin horizontal bars.

Table 3
Adjusted multivariable analyses comparing lung function (age 6 years and older) and nutrition outcomes between South African (SA) and Canadian (CN) CF registry cohorts 2018.

	Lung function ($N = 2877$ CN, 307 SA)[#]		Poor nutrition ($N = 3391$ CN, 404 SA)[#†]	
Variable	Coefficient (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Intercept	90.25 (88.48–92.03)	<0.0001	–	–
Country (SA vs CN)	−8.86 (−11.39–−6.33)	<0.0001	1.70 (1.19–2.41)	0.0076
Sex (Male vs. female)	−1.15 (−2.59–0.30)	0.11	0.88 (0.70–1.11)	0.25
Mutation Class				
I-III	Ref		Ref	
IV- V	5.19 (2.88–7.49)	<0.0001	0.90 (0.58–1.39)	0.60
Missing	−2.20 (−6.13–1.73)	0.27	1.68 (0.92–3.05)	0.082
Age (centered at 18 years)			0.97 (0.96–0.98)	0.00012
*Age-18 – term 1	−685.09 (−733.20–636.98)	<0.0001		
*Age −18 – term 2	221.31 (181.10–261.53)	<0.0001		
Age at diagnosis				
<2 years	Ref		Ref	
2–18 years	1.25 (−0.38–2.88)	0.13	1.25 (0.95–1.64)	0.10
≥ 18 years	11.02 (8.04–13.99)	<0.0001	1.09 (0.57–2.09)	0.78
Any *P.aeruginosa*	−2.88 (−4.47–−1.30)	0.0010	1.21 (0.93–1.56)	0.14
Azithromycin	−9.27 (−10.96–−7.58)	<0.0001	1.43 (1.06–1.91)	0.02
rhDNase	−7.14 (−8.68–−5.61)	<0.0001	1.36 (1.05–1.75)	0.02
Poor nutrition	−16.16 (−18.30–−14.02)	<0.0001	–	

Legend Table 3.
*Age was modeled as a quadratic relationship between age and lung function.
[#]Excluding lung transplant recipients, people started on CFTR modulator therapy before 2018 and children less than 6 years (no lung function recorded).
[†]Lung function excluded from the nutrition modeling to not exclude children less than 6 years without LF measurements.

A strength of this study is it illustrates the value of CF registries and how they can contribute to our understanding of CF epidemiology and outcomes in different global and socioeconomic settings. However, harmonization of registry variables as required in our study is key to meaningful comparisons between different registry populations [23].

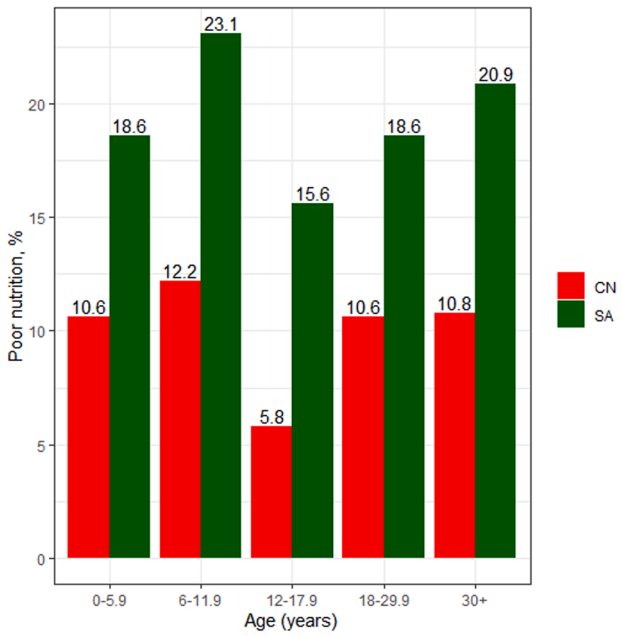

Fig. 3. Proportion (as percentage) of people with CF in the South African and Canadian CF Registry cohorts with poor nutrition in 2018, by age categories. Poor nutrition was defined as BMI z-score < -1 for age < 18 years or BMI < 18.5 kg/m^2 for age 18 years and older; differences between countries in all categories are statistically significant (SMD ≥ 10).

Our study is the first attempt to directly compare CF outcomes between a LMIC and HIC and highlights important disparities after adjusting for known factors and differences in genotype and ancestry characteristics between countries. South Africa shares similarities in CF epidemiology and unequal or limited health care resources with other LMIC. The disparity findings of our study are therefore relevant to other LMIC settings. Poor nutrition across all ages was more prevalent in SA compared to Canada and was the strongest factor negatively impacting LF in the adjusted multivariable analysis. Poor nutrition is an important modifiable aspect of CF care which needs greater attention in SA as similarly demonstrated in previous studies comparing nutrition outcomes between countries [23]. In addition, improved sputum surveillance and more aggressive *P. aeruginosa* treatment is another aspect of CF care which could be improved in SA.

People in LMIC represent 10% of an estimated 105,352 known diagnosed pwCF in 45 countries across the world of which only 12% are receiving triple combination CFTR modulator therapy [24]. However, the hidden global burden of undiagnosed CF disease is uncertain but estimated to be substantially greater than currently known and compounded by a paucity of high-quality data and limited capacity to diagnose CF in many LMIC [24]. Highlighting existing global disparities is especially important at a time when CFTR modulator therapy is rapidly becoming the standard of care in most HIC. Simulated projections of the Canadian CF Registry population have estimated that universal introduction of triple combination CFTR modulator therapy (tezacaftor/-ivacaftor/elexacaftor) in 2021, would by 2030, reduce the number of CF-related deaths by 15% [4]. The delay and unlikely availability of CFTR modulator drugs in LMIC for a long time due to prohibitive pricing and patent protection laws, will undoubtably lead to further widening of global disparities in CF outcomes between LMIC and HIC [25,26]. Ironically, earlier access to CFTR modulator therapy in LMIC will likely lessen the burden and complexity of CF care in LMIC due less severe disease and fewer CF-related complications.

Another disparity highlighted by our study is the absence of NBS for CF in SA and the impact this likely has on explaining the lower nutritional status seen in the SA cohort. Although only 13% of Canadians with CF in 2018 were diagnosed by NBS and median diagnosis age was slightly younger in Canada compared to SA, evidence that NBS improves long-term CF outcomes and survival is unequivocal [27]. Poorer nutrition and LF outcomes were present already in young SA children compared to children in Canada and supports the need to explore the feasibility of NBS for CF in SA. Although challenging and seldom prioritised by governments in LMIC, NBS for CF has been successfully implemented in several LMIC [27–30].

Our study has several limitations which were taken into consideration with interpretation of the findings. First, missing registry data significantly diminished the sample size of the formal analyses which reduced the precision of our estimates. Second, the SA registry data is unlikely to be an exhaustive representation of the CF population in SA as the true incidence, including undiagnosed cases of CF in SA, especially in the non-White population, is unknown. There is insufficient population data to accurately predict the expected incidence of CF in the majority, black African SA population but it is significantly lower than in White and mixed-race populations [31]. Data of the 446 SA patients in this study was extracted from the SA CF registry after its first year of inception in 2018 and is in our view the best representation of the available background diagnosed CF population in SA at the time. Follow-up and retention in the SA registry is high and it is unlikely that there are significant numbers of pwCF receiving care outside the designated CF clinics in SA, nor is it likely that CF-related deaths in SA registry patients were missed. Third, cross-sectional analysis of registry cohorts limit the interpretation of observed age-trends as they cannot be interpreted as average trends of individuals over time. Longitudinal analysis of individual trends over time between SA and Canada will enhance the interpretability of the observed differences observed in this study. Based on established knowledge, we selected variables *a priori* to include in the multivariable models for LF and nutrition outcomes. It is possible that inclusion of more variables such as a wider range of pulmonary infections might alter the overall differences in outcomes between countries due to unmeasured interactions. However, harmonization of all pulmonary infection definitions between the two registries was not possible, thus limiting the inclusion of other infections in the models. A slightly greater proportion of pancreatic sufficient pwCF in Canada compared to SA may be a factor contributing to better nutrition and LF outcomes in Canada. However, the proportional difference of people with pancreatic sufficiency is small and unlikely to be statistically significant. In addition, adjusting for class IV-VI CFTR mutations and older age of diagnosis would have accounted for the differences in proportions of pwCF with milder CF phenotypes with pancreatic sufficiency between the two countries.

In conclusion, this study has demonstrated the value of CF registry-based research and has highlighted important disparities in CF outcomes between a HIC and LMIC settings which has global relevance for countries with similar socioeconomic conditions and challenges impacting on CF care. In addition to improving the quality of established CF care, affordable and equitable global access to CFTR modulators in LMIC must be prioritised in order to reduce the inevitable widening CF outcome disparities between HIC and LMIC that will result from CFTR modulators becoming standard of care in HIC across the world.

We also thank our collaborators on the SA CF registry steering committee whose support helped establish the SA CF Registry:

Name	Affiliation
Dr Paul Gebers	Netcare Greenacres Hospital and Life St George's Hospital, Port Elizabeth
Dr Susan Klugman Dr Cathy Baird	Charlotte Maxeke Academic Hospital, University of the Witwatersrand, Johannesburg.
Dr Tumi Pitso Prof Robin Green	Steve Biko Academic Hospital, University of Pretoria
Dr Cathy Baird	Netcare Milpark Hospital, Johannesburg
Dr Carla Els	Netcare Linksfield Hospital, Johannesburg
Dr Dave Richard	Sandton Medi-Clinic, Johannesburg

(*continued on next page*)

(*continued*)

Name	Affiliation
Prof Refiloe Masekela Dr Reratilwe Mphahlele	Inkosi Albert Luthuli Central Hospital, University of KwaZulul Natal, Durban.
Dr Graham Lawrence	Busamed Hillcrest Private Hospital, Durban
Dr Jonathan Egner	Netcare St Augustine's Hospital, Durban
Dr Fiona Kritzinger Dr Taryn Gray	The Chest and Allergy center; Christian Barnard Memorial Hospital, Cape Town
Dr Julie Morrison Prof Pierre Goussard	Tygerberg Hospital, University of Stellenbosch, Cape Town
Prof Greg Calligaro	Groote Schuur Hospital, University of Cape Town
Prof Paul Wilcox	UCT Private Academic Hospital, Cape Town
Dr Tony Biebuyck	Panorama Medi-Clinic Hospital, Cape Town.

CRediT authorship contribution statement

Marco Zampoli: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Jenna Sykes:** Data curation, Formal analysis, Writing – review & editing. **Janine Verstraete:** Investigation, Data curation, Writing – review & editing. **Stephanie Y. Cheng:** Data curation, Writing – review & editing. **Brenda Morrow:** Supervision, Writing – review & editing. **Michael S. Pepper:** Conceptualization, Writing – review & editing. **Cheryl Stewart:** Writing – review & editing. **Heather J. Zar:** Supervision. **Anne L. Stephenson:** Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

None.

Acknowledgments

We thank the Canadian and SA CF Registry Steering Committees and registry collaborators for generously supporting this study and contributing, extracting, and sharing their respective registry datasets. We would also like to acknowledge the involvement and continued participation of individuals living with CF who consent to having their data submitted and used for research purposes. M Zampoli's and J Verstraete work is supported by the Cystic Fibrosis Foundation (ZAMPOLI9KO), the SA CF Association and the Harry Crossley Foundation. B. Morrow's work is partly supported by the National Research Foundation of South Africa. M Pepper's work is supported by the South African Medical Research Council and the SA National Research Foundation.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2023.09.003.

References

[1] Jackson AD, Goss CH. Epidemiology of CF: how registries can be used to advance our understanding of the CF population. J Cyst Fibros 2018;17(3):297–305.
[2] Keogh RH, Stanojevic S. A guide to interpreting estimated median age of survival in cystic fibrosis patient registry reports. J Cyst Fibros 2018;17(2):213–7.
[3] Keating D, Marigowda G, Burr L, Daines C, Mall MA, McKone EF, Ramsey BW, Rowe SM, Sass LA, Tullis E, et al. VX-445-tezacaftor-ivacaftor in patients with cystic fibrosis and one or two Phe508del alleles. N Engl J Med 2018;379(17):1612–20.
[4] Stanojevic S, Vukovojac K, Sykes J, Ratjen F, Tullis E, Stephenson AL. Projecting the impact of delayed access to elexacaftor/tezacaftor/ivacaftor for people with cystic fibrosis. J Cyst Fibrosis 2021;20(2):243–9.
[5] Bell SC, Mall MA, Gutierrez H, Macek M, Madge S, Davies JC, Burgel PR, Tullis E, Castanos C, Castellani C, et al. The future of cystic fibrosis care: a global perspective. Lancet Respir Med 2020;8(1):65–124.
[6] da Silva LVRF, Maróstica PJC, Athanazio RA, Reis FJC, Damaceno N, Paes AT, Hira AY, Schlesinger D, Kok F, Amaral MD. Extensive CFTR sequencing through NGS in Brazilian individuals with cystic fibrosis: unravelling regional discrepancies in the country. J Cyst Fibrosis 2020. published ahead of print available at, https://doi.org/10.1016/j.jcf.2020.08.007. accessed 19 September 2020.
[7] Stewart C, Pepper MS. Cystic fibrosis on the African continent. Genet Med 2016;18(7):653–62.
[8] Worldometer; available at https://www.worldometers.info/world-population/south-africa-population/; accesssed 25 April 2020.
[9] Zampoli M, Verstraete J, Frauendorf M, Kassanjee R, Workman L, Morrow BM, Zar HJ. Cystic fibrosis in South Africa: spectrum of disease and determinants of outcome. ERJ Open Res 2021;7(3).
[10] Zampoli M, Kassanjee R, Verstraete J, Westwood A, Zar HJ, Morrow BM. Trends in cystic fibrosis survival over 40 years in South Africa: an observational cohort study. Pediatr Pulmonol 2022;57(4):908–18.
[11] Fink AK, Loeffler DR, Marshall BC, Goss CH, Morgan WJ. Data that empower: the success and promise of CF patient registries. Pediatr Pulmonol 2017;52(S48):S44–51.
[12] Stephenson AL, Sykes J, Stanojevic S, Quon BS, Marshall BC, Petren K, Ostrenga J, Fink AK, Elbert A, Goss CH. Survival comparison of patients with cystic fibrosis in Canada and the United States: a population-based cohort study. Ann Intern Med 2017;166(8):537–46.
[13] Stephenson AL, Ramos KJ, Sykes J, Ma X, Stanojevic S, Quon BS, Marshall BC, Petren K, Ostrenga JS, Fink AK. Bridging the survival gap in cystic fibrosis: an investigation of lung transplant outcomes in Canada and the United States. J Heart Lung Transpl 2021;40(3):201–9.
[14] Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40(6):1324–43.
[15] Smith S.J., Gray D.M., MacGinty R.P., Hall G.L., Stanojevic S., Mphahlele R., Masekela R. Medicine cc. Choosing the better global lung initiative 2012 equation in South African population groups. 2020;202(12):1724–7.
[16] WHO AnthroPlus for personal computers manual: software for assessing growth of the world's children and adolescents. Geneva: WHO, 2009 available at: http://www.who.int/growthref/tools/en/.
[17] Normand SLT, Landrum MB, Guadagnoli E, Ayanian JZ, Ryan TJ, Cleary PD, McNeil BJ. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. J Clin Epidemiol 2001;54(4):387–98.
[18] Toutenburg H, Rubin DB. Multiple imputation for nonresponse in surveys. New York: Wiley; 1987. XXIX+ 258 pp. In: Springer; 1990.
[19] McKone EF, Ariti C, Jackson A, Zolin A, Carr SB, Orenti A, van Rens JG, Lemonnier L, Macek M, Keogh RH, et al. Survival estimates in European cystic fibrosis patients and the impact of socioeconomic factors: a retrospective registry cohort study. Eur Respir J 2021;58(3).
[20] Oates GR, Schechter MS. Social inequities and cystic fibrosis outcomes: we can do better. Ann Am Thorac Soc. 2021;18(2):215–7.
[21] World bank GDP per capita data: avaialble at: https://data.worldbank.org/indicator/NY.GDP.PCAP.CD; accessed 19 May 2023.
[22] McIntyre K, Bertrand DP, Rault G. Using registry data to improve quality of care. J Cyst Fibrosis 2018;17(5):566–72.
[23] Goss CH, Sykes J, Stanojevic S, Marshall B, Petren K, Ostrenga J, Fink A, Elbert A, Quon BS, Stephenson AL. Comparison of nutrition and lung function outcomes in patients with cystic fibrosis living in Canada and the United States. Am J Respir Crit Care Med 2018;197(6):768–75.
[24] Guo J, Garratt A, Hill A. Worldwide rates of diagnosis and effective treatment for cystic fibrosis. J Cyst Fibros 2022;21(3):456–62.
[25] Guo J, Wang J, Zhang J, Fortunak J, Hill A. Current prices versus minimum costs of production for CFTR modulators. J Cyst Fibros 2022;21(5):866–72.
[26] Robbins S.N.R. 2023 Miracle cystic fibrosis drug kept out of reach in developing countries; available at: https://www.nytimes.com/2023/02/07/health/cystic-fibrosis-drug-trikafta.html?smid=url-share. New York Times 72023 7 February.
[27] Scotet V, Gutierrez H, Farrell PM. Newborn screening for CF across the globe—where is it worthwhile? Int J Neonatal Screen 2020;6(1):18.
[28] Nunes LM, Ribeiro R, Niewiadonski VDT, Sabino E, Yamamoto GL, Bertola DR, Gaburo N, da S, Filho L. A new insight into CFTR allele frequency in Brazil through next generation sequencing. Pediatr Pulmonol 2017;52(10):1300–5.
[29] Padilla CD, Therrell BL, Alcausin MMLB, Chiong MAD, Abacan MAR, Reyes MEL, Jomento CM, Dizon-Escoreal MTT, Canlas MAE, Abadingo ME. Successful Implementation of Expanded Newborn Screening in the Philippines Using Tandem Mass Spectrometry. Int J Neonatal Screen 2022;8(1):8.
[30] Sasihuseyinoglu A, Altintaş D, Bişgin A, Doğruel D, Yilmaz M, Serbes M. Two years of newborn screening for cystic fibrosis in Turkey: çukurova experience. Turk J Pediatr 2019;61(4).
[31] Padoa C, Goldman A, Jenkins T, Ramsay M. Cystic fibrosis carrier frequencies in populations of African origin. J Med Genet 1999;36(1):41–4.